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Consumption of Alcoholic and Sugar-Sweetened Beverages is Associated with Increased Liver Fat Content in Middle-Aged Men and Women

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ABSTRACT

Background: Fatty liver is the leading cause of chronic liver diseases and increases the risk of cardiovascular disease. Besides alcohol consumption, energy-containing nonalcoholic beverages may contribute to liver fat accumulation.

Objective: We aimed to study the consumption of alcoholic and nonalcoholic beverages and their mutual replacement in relation to hepatic triglyceride content (HTGC) in middle-aged men and women.

Methods: In this cross-sectional analysis, HTGC was assessed by proton magnetic resonance spectroscopy. Habitual consumption of alcoholic and nonalcoholic beverages was assessed using a validated food-frequency questionnaire. All beverages were converted to standard servings and to percentage of total energy intake (En%). We performed linear regression to examine the association of alcoholic and nonalcoholic beverages with HTGC, adjusted for age, sex, smoking, education, ethnicity, physical activity, total energy intake, and total body fat. We studied replacement of alcoholic beverages with nonalcoholic beverages per 1 serving/d and per 5 En%/d.

Results: After exclusion of individuals with missing values, 1966 participants (47% men) were analyzed, with a mean ± SD age of 55 ± 6 y, BMI of 26 ± 4 kg/m^2, and HTGC of 5.7% ± 7.9%. Each extra alcoholic serving per day was associated with more liver fat (1.09 times; 95% CI: 1.05, 1.12). Replacing 5 En% of alcoholic beverages with milk was associated with less liver fat (0.89 times; 95% CI: 0.81, 0.98), whereas replacement with 5 En% of sugar-sweetened beverages was associated with liver fat to an extent similar to alcoholic beverages (1.00 times; 95% CI: 0.91, 1.09).

Conclusion: In a population-based cohort, consumption of each extra daily alcoholic beverage was associated with more liver fat. In isocaloric replacement of alcoholic beverages, milk was associated with less liver fat, whereas sugar-sweetened beverages were equally associated with liver fat. This suggests that intake of alcohol and sugars may contribute to liver fat accumulation. This trial was registered at clinicaltrials.gov as NCT03410316. *J Nutr* 2019;149:649–658.

Keywords: alcohol consumption, liver fat, substitution, alcoholic beverages, nonalcoholic beverages

Introduction

Nonalcoholic fatty liver disease (NAFLD) is often defined as a hepatic TG content (HTGC) of >5.56% not due to excessive alcohol consumption (1). NAFLD covers a broad clinical spectrum, ranging from the most common feature, hepatic steatosis, to nonalcoholic steatohepatitis (NASH) and liver cirrhosis (2), and increases the risk of end-stage liver disease and liver-related and all-cause mortality (3–6). Although the incidence of NAFLD is underreported and varies widely (7), the prevalence has risen considerably over the last 2 decades (8) to 14–34% of the general population in Europe (9, 10), Asia (11), and the United States (7, 11). The prevalence of NAFLD in obesity might even be as high as 90% (12), possibly due to excessive calorie intake (13). It is the leading cause of chronic liver diseases worldwide (14) and is also strongly associated with the metabolic syndrome (15) and cardiovascular diseases (16).

Excessive alcohol consumption (17) is a well-established risk factor for both hepatic steatosis (liver fattening) and liver disease. Current guidelines to prevent or reduce liver

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fat accumulation therefore recommend that heavy alcohol consumption should be discouraged (18). However, there is much controversy over whether moderate alcohol consumption should also be discouraged, because there are studies indicating that light to moderate alcohol consumption might be protective in relation to fatty liver and (extra)hepatic complications (18–23), whereas in a Mendelian randomization study it has been suggested there is no beneficial effect of moderate alcohol consumption on the severity of NAFLD (24). Moreover, it has been shown that liquid food leads to less satiety and more postprandial hunger (25). Alcohol in particular is very inefficient in activating the satiety mechanism and consuming alcohol during meals might lead to higher food consumption (26).

In addition, sugar-sweetened beverages (SSBs), but not diet sodas, have been associated with fatty liver (27). This suggests that energy-containing drinks in general, or specifically dietary sugars, may increase liver fat as well (28, 29). As the relative contributions of different types of nonalcoholic and alcoholic beverage consumption to liver fat accumulation remain unclear, we aimed to directly compare the associations of consumption of alcoholic beverages and nonalcoholic energy-containing and non–energy-containing beverages with HTGC in a large sample of the general population. Insight into these associations may contribute to lifestyle guidelines, especially with regard to beverages, for both primary and secondary prevention aims.

Methods

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort study in 6671 individuals aged 45–65 y, with an oversampling of persons with a BMI (in kg/m^2) of ≥27. Men and women aged between 45 and 65 y with a self-reported BMI of ≥27 living in the greater area of Leiden (in the west of the Netherlands) were eligible to participate in the NEO study. In addition, all inhabitants aged between 45 and 65 y from 1 municipality (Leiderdorp) were invited irrespective of their BMI, allowing for a reference distribution of BMI. Detailed information about the study design and data collection has been described elsewhere (30).

The present study is a cross-sectional analysis of the baseline measurements of the participants with a measurement of HTGC. For our analyses we excluded participants with an implausibly high or low total energy intake (<600 kcal or >5000 kcal) and missing data on beverage consumption or potential confounding factors.

The study was approved by the medical ethics committee of the Leiden University Medical Center and all participants gave written informed consent.

Beverage consumption

Habitual consumption of beverages of all participants was estimated using a semiquantitative FFQ, which was originally designed to study dietary fat intake (31, 32). Consumption of alcoholic and nonalcoholic beverages was assessed in absolute frequency (times per day, week, and month). Participants were asked about consumption of different alcoholic beverages (beer, wine, liquor, and mixed drinks such as cocktails). For each alcoholic beverage we used a standard serving based on the Dutch Food Composition Database (NEVO-2011): 200 g for beer, 110 g for wine, 50 g for liquor, and 258 g for mixed long drinks, so that each consumption contained 10 g of alcohol. Nonalcoholic beverages were also converted to standard servings: 200 g for nonalcoholic beers, 125 g for coffee and tea, 150 g for milk, and 150 g for SSBs (NEVO-2011). Nonalcoholic beverages were divided into energy-containing (nonalcoholic beers, milk, and SSBs) or non-energy-containing (tea and coffee without milk) beverages. No information on water consumption or diet sodas was collected using the FFQ. After the conversion to standard servings, all nonalcoholic beverages were also summed up into 1 variable. The same was done for all alcoholic beverages. Total alcoholic beverage consumption was divided into subcategories: 0–0.5 g alcohol/d (including abstainers), 0.5–5 g/d, 5–15 g/d for women and 5–30 g/d for men, and lastly >15 g/d for women and >30 g/d for men.

We assessed the reproducibility of the habitual consumption of different beverages in a random subgroup of 100 participants who completed the FFQ for a second time ∼3 mo after the baseline measurement. The individual measurement intraclass correlation coefficients of the different beverages were 0.63 for SSBs, 0.81 for milk, 0.82 for coffee, 0.91 for tea, 0.79 for beer, 0.82 for wine, 0.67 for mixed drinks, and 0.89 for liquor, which can be considered good to excellent (33).

Proton magnetic resonance spectroscopy of liver fat content

Proton magnetic resonance spectroscopy (^{1}H-MRS) of the liver was performed on a 1.5 Tesla whole-body MR scanner (Philips Medical Systems) and spectra were obtained as described previously (34). ^{1}H-MRS data were fitted using Java-based magnetic resonance user interface software (jMRUI version 2.2) (35). HTGC relative to water was calculated as follows: (signal amplitude of TG)/(signal amplitude of water) × 100.

Data collection of covariates

In the baseline questionnaire, participants reported smoking behavior in 3 categories: current, former, or never smoking (reference group). Ethnicity was reported by self-identification in 8 categories which we grouped into white (reference group) and other. Highest level of education was reported in 10 categories according to the Dutch education system and grouped into high (including higher vocational school, university, and postgraduate education) and low education (reference group). Physical activity during leisure time was reported using the Short Questionnaire to Assess Health-Enhancing Physical Activity and was expressed in metabolic equivalent of task–hours per week (36). Data collection on other covariates has been described previously (30).

Statistical analyses

In the NEO study there is an oversampling of persons with a BMI of ≥27. To correctly represent associations in the general population (37), adjustments for this oversampling were made. This was done by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality (38), whose BMI distribution was similar to the BMI distribution of the general Dutch population (39)

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Abbreviations used: En%, percent(age) of total energy intake; ^{1}H-MRS, proton magnetic resonance spectroscopy; HTGC, hepatic TG content; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NEO, Netherlands Epidemiology of Obesity study; *PNPLA3*, patatin-like phospholipase domain-containing protein 3; SSB, sugar-sweetened beverage.

(**Supplemental Table 1**, **Supplemental Figure 1**). All results were based on weighted analyses. Consequently, the results apply to a population-based study without oversampling of individuals with a BMI ≥27. As a result of the weighting, only percentages and proportions can be given instead of numbers of participants. Baseline characteristics are displayed in percentages or means ± SDs for the total population, and stratified by sex and categories of alcohol consumption.

We performed linear regression analyses to examine the association between alcohol consumption and liver fat. We performed 3 different models and also stratified each model by sex, owing to the known differences in both alcohol consumption and liver fat content between men and women. Because of the skewed distribution of HTGC, we used the natural logarithm of this variable in the analyses. For easier interpretation of these results, we back transformed the regression coefficients towards a ratio [using exp(β)] with a 95% CI. Such a ratio, for example 1.2, can be interpreted as 1.2 times HTGC for each extra serving per day, which would reflect an increase in HTGC from, for example, 5% to 6%. We first performed linear regression analysis to examine the association of alcohol consumption as a categorical variable [0–0.5 g/d (reference), ≥0.5–5 g/d, ≥5–15 g/d for women and ≥5–30 g/d for men, and ≥15 g/d for women and ≥30 g/d for men] with HTGC. We tested for a linear trend (P = 0.01) and also added a quadratic term (P = 0.49) to the model to check for nonlinearity.

Then, we studied alcohol consumption as a continuous outcome in 3 different ways. Firstly, we studied the association between 1 serving of alcohol (total alcohol, beer, wine, mixed drinks, and liquor) and 1 serving of nonalcoholic beverages (SSBs, milk, coffee, tea, and nonalcoholic beer) per day and liver fat content. This was done in both a crude model and a multivariable linear regression model, which was adjusted for age, sex, smoking, education, ethnicity, physical activity, and total energy intake. Models studying separate alcoholic beverages were also adjusted for all other alcoholic beverages, and models on nonalcoholic beverages were also adjusted for all other nonalcoholic beverages.

Secondly, we studied the effect of substituting 1 serving of an alcoholic beverage with 1 serving of a nonalcoholic beverage. In these substitution models we included a sum variable of all beverages, in addition to each beverage separately, except for the beverage to be substituted, in this case alcoholic beverages. Instead of total energy intake, these substitution models were adjusted for caloric intake from food only, to adjust for possible confounding when substituting different beverages. Accordingly, the regression coefficients can be interpreted as the relative change in HTGC if 1 serving/d of an alcoholic beverage was substituted by 1 serving/d of a nonalcoholic beverage.

Thirdly, in addition to the substitution analyses based on servings, we also performed an isocaloric substitution model replacing alcoholic beverages with energy-containing nonalcoholic beverages. This model was adjusted for both caloric intake from beverages and caloric intake from food. In these analyses 5% of total energy intake (En%) from alcoholic beverages is replaced with 5 En% from energy-containing nonalcoholic beverages (SSBs, milk, and nonalcoholic beer) in relation to HTGC, to examine to what extent the caloric content contributes to liver fat content. To study whether the associations are specific for liver fat, we also adjusted all 3 models for total body fat.

To examine to what extent consumption of alcoholic beverages was associated with liver fat content in participants without a fatty liver, we stratified the analyses by the arbitrary cutoff of 5.56% which indicates a fatty liver. Next, we stratified by the rs738409 single nucleotide polymorphism in the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene that is associated with diffuse fat deposition in the liver and may promote NASH, fibrosis, and cirrhosis throughout the liver (40), to investigate whether the associations differ between carriers and noncarriers of the single nucleotide polymorphism.

As a means of undertaking sensitivity analyses, we repeated the substitution analysis based on servings after taking into account the milk and sugar potentially added to coffee and tea. In the analyses with categories of alcohol consumption, we repeated the analyses after excluding alcohol abstainers (0 g/d) from the reference group. In addition, we performed the models after exclusion of participants with type 2 diabetes or cardiovascular disease, because they might have changed their drinking habits after being diagnosed, or might potentially react differently to sugars.

All the aforementioned analyses were predefined, and analyses not prespecified are considered exploratory. We performed all analyses using Stata statistical software (Statacorp) version 14.

Results

In total, 6671 participants were included in the NEO study between September, 2008 and October, 2012, of whom 2580 underwent a liver fat measurement by ^{1}H-MRS. However, the limited time slot that was available per participant did not allow time for a repeat examination when technical failures were present (n = 497), leaving 2083 participants with a successful liver fat measurement. After exclusion of participants with extreme energy intake (n = 18), missing dietary data (n = 26), missing data on potential confounding factors (n = 1 for smoking, n = 16 for education, n = 2 for ethnicity, n = 44 for physical activity in leisure time, n = 3 for total body fat, and n = 6 for visceral adipose tissue), and 1 participant for whom the log transformation of the liver fat could not be calculated, 1,966 participants were included in the analyses. Baseline characteristics of these participants are presented in **Table 1**. Participants with higher alcohol consumption were more often smokers and had on average a higher education. HTGC and the prevalence of a fatty liver were also higher in the categories with higher alcohol consumption. Whereas men on average have a higher coffee and beer consumption, women have a higher tea consumption.

Table 2 displays the association between different categories of alcohol consumption and liver fat content. Despite a linear trend (P-trend = 0.01), light and moderate consumption were not significantly associated with liver fat (Table 2). Compared with no alcohol consumption (0–0.5 g/d), high alcohol consumption (>15 g/d for women and >30 g/d for men) was associated with more liver fat, for total alcohol consumption (1.28 times; 95% CI: 1.06, 1.55), beer consumption (1.39 times; 95% CI: 1.08, 1.80), and wine consumption (1.28 times; 95% CI: 1.04, 1.58) (Table 2). Results were similar when excluding alcohol abstainers (0 g/d) from the reference group (data not shown).

Table 3 shows the associations between consumption of different alcoholic beverages as continuous variables and liver fat content. Each extra alcoholic serving was associated with more liver fat (1.09 times; 95% CI: 1.06; 1.13). When also adjusted for total body fat to examine whether the associations were specific for liver fat, associations attenuated for liquor and mixed drinks, although total alcoholic beverages remained associated with more liver fat (1.09 times; 95% CI: 1.05, 1.12).

The associations of nonalcoholic beverages are shown in **Table 4**. In the total population, each extra serving of nonalcoholic beverages was associated with less liver fat (0.97 times; 95% CI: 0.95, 0.99). Consumption of coffee (0.96 times for each extra serving; 95% CI: 0.93, 0.99), tea (0.97 times; 95% CI: 0.94, 1.00), and milk (0.95 times; 95% CI: 0.89, 1.00) were also associated with less liver fat. Results did not differ after exclusion of participants with type 2 diabetes or cardiovascular disease or when taking the milk and sugar added to coffee and tea into account (data not shown).

TABLE 1 Characteristics of participants of the Netherlands Epidemiology of Obesity study, men and women between 45 and 65 y of age with direct assessment of HTGC by proton magnetic resonance spectroscopy[1]

				Alcohol consumption			
	Total population	Men (47%)	Women (53%)	0–0.5 g/d (16%)	>0.5–5 g/d (21%)	>5–15 g/d women >5–30 g/d men (38%)	>15 g/d women >30 g/d men (24%)
Age, y	55 ± 6	56 ± 6	55 ± 6	55 ± 7	55 ± 6	56 ± 6	56 ± 6
Sex, men	47	—	—	30	34	60	44
Ethnicity, white	96	96	96	92	93	97	99
Education, high	46	51	42	32	41	50	55
Smoking, current	14	16	13	13	7	13	23
Physical activity in leisure time, MET h/wk	37.8 ± 31.9	39.1 ± 37.1	36.7 ± 27.3	38.6 ± 38.4	35.3 ± 28.0	38.4 ± 31.9	38.9 ± 31.4
SSBs,[2] servings/d	0.8 ± 1.0	0.9 ± 1.1	0.8 ± 0.9	1.1 ± 1.4	0.9 ± 1.0	0.8 ± 0.8	0.8 ± 0.9
Milk,[2] servings/d	1.1 ± 1.0	1.2 ± 1.2	0.9 ± 0.9	1.1 ± 1.2	1.1 ± 1.0	1.0 ± 0.9	1.0 ± 1.1
Coffee,[2] servings/d	3.7 ± 2.1	4.3 ± 2.4	3.2 ± 1.8	3.3 ± 2.4	3.1 ± 2.0	4.0 ± 2.1	4.0 ± 2.1
Tea,[2] servings/d	2.0 ± 1.9	1.4 ± 1.7	2.4 ± 2.0	2.1 ± 2.2	2.3 ± 1.9	1.8 ± 1.7	1.7 ± 2.1
Nonalcoholic beer,[2] servings/d	0.0 ± 0.2	0.0 ± 0.2	0.0 ± 0.1	0.0 ± 0.2	0.0 ± 0.1	0.0 ± 0.2	0.0 ± 0.1
CVD	5	5	4	8	4	3	5
Diabetes	3	4	2	7	2	2	3
BMI, kg/m^2	25.9 ± 3.9	26.6 ± 3.5	25.2 ± 4.0	26.5 ± 5.0	25.6 ± 4.1	25.8 ± 3.3	25.9 ± 4.1
Waist circumference, cm	91.0 ± 12.6	97.5 ± 10.7	85.4 ± 11.3	91.0 ± 15.1	89.6 ± 11.8	91.4 ± 11.6	91.5 ± 13.7
Total body fat, %	30.7 ± 8.2	24.6 ± 5.7	36.1 ± 6.0	34.3 ± 8.8	31.9 ± 8.6	28.6 ± 7.6	31.3 ± 7.7
VAT, cm^2	88.6 ± 55.1	114.5 ± 60.0	65.9 ± 39.8	85.1 ± 60.0	81.5 ± 49.5	89.9 ± 52.2	95.0 ± 61.3
HTGC, %	5.7 ± 7.9	7.0 ± 8.3	4.6 ± 7.3	5.4 ± 8.2	5.0 ± 7.4	5.5 ± 6.9	6.8 ± 9.5
HTGC > 5.56%	29	39	21	25	24	29	35
Fasting serum TGs, mmol/L	1.2 ± 0.8	1.4 ± 1.0	1.1 ± 0.7	1.2 ± 0.8	1.2 ± 0.8	1.3 ± 0.8	1.3 ± 1.0

[1] Values are means ± SDs or percentages. Results are based on analyses weighted toward the BMI distribution of the general population (n = 1,966). CVD, cardiovascular disease; HTGC, hepatic TG content; MET, metabolic equivalent of task; SSB, sugar-sweetened beverage; VAT, visceral adipose tissue.

[2] Servings equal 150 g for SSBs, 150 g for milk, 125 g for coffee and tea, and 200 g for nonalcoholic beers.

TABLE 2 Relative change in HTGC and 95% CIs for different categories of alcohol consumption in participants of the Netherlands Epidemiology of Obesity study, men and women between 45 and 65 y of age with direct assessment of HTGC by proton magnetic resonance spectroscopy[1]

	0–0.5 g/d	≥0.5–5 g/d	≥5–15 g/d women ≥5–30 g/d men	≥15 g/d women ≥30 g/d men	*P*-trend
Alcohol (total)					
Multivariable-adjusted[2] relative change (95% CI)	1 (ref)	1.05 (0.87, 1.25)	1.07 (0.90, 1.28)	1.28 (1.06, 1.55)	0.01
Proportion of population, %	13.7	22.2	41.0	23.1	
Beer[3]					
Multivariable-adjusted relative change (95% CI)	1 (ref)	0.94 (0.83, 1.08)	1.10 (0.93, 1.29)	1.39 (1.08, 1.80)	0.03
%	48.1	27.5	18.5	6.0	
Wine[3]					
Multivariable-adjusted relative change (95% CI)	1 (ref)	1.01 (0.88, 1.16)	1.02 (0.89, 1.18)	1.28 (1.04, 1.58)	0.16
%	23.3	32.7	34.8	9.3	

[1] HTGC, hepatic TG content.
[2] Adjusted for age, sex, smoking, education, ethnicity, physical activity in leisure time, total energy intake, and total body fat. Results are based on analyses weighted towards the BMI distribution of the general population ($n = 1,966$), derived from β coefficients with 95% CIs from linear regression analyses and expressed as a relative change compared with the reference category. Such a ratio, for example 1.2, can be interpreted as 1.2 times HTGC for each extra serving per day, which would reflect an increase in HTGC from, for example, 5% to 6%.
[3] Also adjusted for other alcoholic beverages. Servings equal 200 g for beer and 110 g for wine.

Table 5 shows that substituting 1 alcoholic serving with 1 nonalcoholic serving was associated with less liver fat (0.90 times; 95% CI: 0.86, 0.94) in the total population after adjustment for potential confounding factors and total body fat. Of the different nonalcoholic beverages, replacement with milk (0.88 times; 95% CI: 0.82, 0.95), tea (0.89 times; 95% CI: 0.85, 0.94), and coffee (0.88 times; 95% CI: 0.84, 0.92) were all associated with less liver fat. Results were similar when taking the milk and sugar added to coffee and tea into account (data not shown).

Isocaloric substitution of 5 En% from alcoholic beverages with 5 En% from nonalcoholic beverages (Table 6) showed that substitution of alcohol with milk was associated with less HTGC (0.89 times; 95% CI: 0.81, 0.98) in the total population. Replacing 5 En% from alcohol with 5 En% from SSBs was associated with liver fat equally strongly as was alcohol (1.00 times; 95% CI: 0.91, 1.09).

After stratifying the analyses by the cutoff of fatty liver (HTGC >5.56%), associations between alcohol consumption and liver fat were similar in both groups (**Supplemental Table**

TABLE 3 Relative change in HTGC and 95% CIs per 1 serving/d higher consumption of alcoholic beverages in participants of the Netherlands Epidemiology of Obesity study, men and women between 45 and 65 y of age with direct assessment of HTGC by proton magnetic resonance spectroscopy[1]

	Crude	Multivariable	Multivariable + TBF
Total alcohol			
Total	1.15 (1.11, 1.19)	1.09 (1.06, 1.13)	1.09 (1.05, 1.12)
Men	1.11 (1.07, 1.15)	1.11 (1.07, 1.15)	1.09 (1.05, 1.13)
Women	1.05 (0.97, 1.14)	1.09 (1.00, 1.18)	1.10 (1.02, 1.19)
Beer[2]			
Total	1.14 (1.09, 1.19)	1.07 (1.02, 1.11)	1.08 (1.03, 1.13)
Men	1.08 (1.04, 1.13)	1.08 (1.04, 1.13)	1.09 (1.04, 1.15)
Women	0.95 (0.84, 1.07)	1.02 (0.89, 1.17)	1.06 (0.96, 1.17)
Wine[2]			
Total	1.13 (1.06, 1.20)	1.13 (1.06, 1.21)	1.11 (1.05, 1.18)
Men	1.13 (1.06, 1.21)	1.13 (1.06, 1.21)	1.08 (1.02, 1.15)
Women	1.12 (1.02, 1.24)	1.13 (1.02, 1.26)	1.15 (1.04, 1.28)
Liquor[2]			
Total	1.64 (1.45, 1.86)	1.22 (1.08, 1.38)	1.06 (0.93, 1.21)
Men	1.33 (1.17, 1.50)	1.24 (1.10, 1.40)	1.10 (0.97, 1.26)
Women	1.28 (0.66, 2.48)	0.95 (0.52, 1.73)	0.62 (0.37, 1.04)
Mixed drinks[2]			
Total	1.56 (1.34, 1.83)	1.18 (1.00, 1.40)	0.97 (0.83, 1.15)
Men	1.26 (1.09, 1.47)	1.18 (1.00, 1.40)	0.98 (0.83, 1.16)
Women	1.74 (0.95, 3.20)	1.53 (0.86, 2.71)	1.12 (0.63, 1.97)

[1] Multivariable analyses adjusted for age, sex, smoking, education, ethnicity, physical activity in leisure time, and total energy intake. Results are based on analyses weighted towards the BMI distribution of the general population ($n = 1,966$), derived from β coefficients with 95% CIs from linear regression analyses and expressed as a relative change. Such a ratio, for example 1.2, can be interpreted as 1.2 times HTGC for each extra serving per day, which would reflect an increase in HTGC from, for example, 5% to 6%. HTGC, hepatic TG content; TBF, total body fat.
[2] Also adjusted for other alcoholic beverages. Servings equal 200 g for beer, 110 g for wine, 50 g for liquor, and 258 g for mixed drinks.

TABLE 4 Relative change in HTGC and 95% CIs per 1 serving/d higher consumption of nonalcoholic beverages in participants of the Netherlands Epidemiology of Obesity study, men and women between 45 and 65 y of age with direct assessment of HTGC by proton magnetic resonance spectroscopy[1]

	Crude	Multivariable	Multivariable + TBF
Total nonalcoholic beverages			
Total	0.98 (0.95, 1.00)	0.97 (0.94, 0.99)	0.97 (0.95, 0.99)
Men	0.98 (0.95, 1.01)	0.99 (0.95, 1.02)	0.98 (0.95, 1.01)
Women	0.95 (0.91, 0.98)	0.94 (0.91, 0.97)	0.95 (0.92, 0.98)
SSBs[2]			
Total	1.07 (1.01, 1.14)	1.05 (0.99, 1.11)	1.03 (0.98, 1.08)
Men	1.04 (0.97, 1.12)	1.07 (0.99, 1.15)	1.02 (0.96, 1.09)
Women	1.05 (0.96, 1.14)	1.02 (0.93, 1.11)	1.03 (0.95, 1.11)
Milk[2]			
Total	1.00 (0.94, 1.07)	0.94 (0.88, 1.00)	0.95 (0.89, 1.00)
Men	0.92 (0.86, 1.00)	0.91 (0.84, 0.99)	0.92 (0.86, 0.99)
Women	1.02 (0.91, 1.13)	0.96 (0.87, 1.07)	0.97 (0.89, 1.06)
Coffee (without sugar or milk)[2]			
Total	1.01 (0.98, 1.04)	0.96 (0.93, 0.99)	0.96 (0.93, 0.99)
Men	1.00 (0.96, 1.04)	0.99 (0.95, 1.03)	0.99 (0.95, 1.02)
Women	0.95 (0.91, 0.99)	0.92 (0.88, 0.96)	0.92 (0.88, 0.96)
Tea (without sugar or milk)[2]			
Total	0.92 (0.89, 0.95)	0.96 (0.92, 0.99)	0.97 (0.94, 1.00)
Men	0.96 (0.92, 1.02)	0.98 (0.93, 1.03)	1.00 (0.94, 1.05)
Women	0.95 (0.92, 0.99)	0.94 (0.90, 0.98)	0.95 (0.91, 0.99)
Nonalcoholic beer[2]			
Total	1.35 (0.99, 1.84)	1.13 (0.88, 1.45)	1.09 (0.86, 1.38)
Men	1.22 (0.90, 1.65)	1.18 (0.89, 1.57)	1.17 (0.90, 1.52)
Women	0.82 (0.40, 1.70)	0.88 (0.49, 1.59)	0.73 (0.49, 1.10)

[1] Multivariable analyses adjusted for age, sex, smoking, education, ethnicity, physical activity in leisure time, and total energy intake. Results are based on analyses weighted towards the BMI distribution of the general population (n = 1,966), and derived from β coefficients with 95% CIs from linear regression analyses and expressed as a relative change. Such a ratio, for example 1.2, can be interpreted as 1.2 times HTGC for each extra serving per day, which would reflect an increase in HTGC from, for example, 5% to 6%. HTGC, hepatic TG content; SSB, sugar-sweetened beverage; TBF, total body fat.

[2] Also adjusted for all other nonalcoholic beverages. Servings equal 150 g for SSBs, 150 g for milk, 125 g for tea and coffee, and 200 g for nonalcoholic beer.

2). Regarding the *PNPLA3* polymorphism, the association between each alcoholic beverage and HTGC was similar in both groups (1.14 times for each extra alcoholic serving; 95% CI: 1.07, 1.21 for GC and GG carriers; and 1.09 times; 95% CI: 1.04, 1.15 for CC carriers).

Discussion

In this population-based cohort of 1,966 middle-aged men and women with directly assessed liver fat content, consumption of each extra alcoholic serving per day was associated with more liver fat, with larger increases in liver fat with excessive alcohol consumption. Replacing 1 alcoholic beverage with 1 nonalcoholic beverage was associated with less liver fat. Whereas isocaloric replacement of alcohol with milk was associated with less liver fat, isocaloric replacement with SSBs was equally associated with liver fat.

This study was conducted within a large cohort study, in which HTGC was directly assessed by ^{1}H-MRS. We used substitution analysis to directly compare different types of beverages and their association with liver fat to each other. The comparative nature of our study can contribute to translation to recommendations in clinical practice, as we have shown that consumption of both alcohol and SSBs is associated with more liver fat, whereas milk, tea, and coffee are associated with less liver fat. More importantly, replacing alcohol with SSBs is therefore equally associated with liver fat, and replacing it with milk, tea, or coffee is associated with less liver fat. This can be translated into clear advice for patients diagnosed with fatty liver and who are advised to stop consuming alcohol. Lastly, extensive phenotype measurements have been performed, allowing adjustment for many potential confounding factors. However, an inherent limitation of the observational cross-sectional design is that we cannot exclude residual confounding by lifestyle factors.

Due to the cross-sectional design, another limitation of this substitution analysis is that it is modelled on a group level rather than on an individual level. All participants completed a semiquantitative FFQ, based on which we estimated the habitual beverage consumption. Although alcohol consumption might have been misreported, intraclass correlations of the beverages showed good to excellent reproducibility. Moreover, by adjusting our analyses for total energy intake we partly corrected for potential misreporting. A limitation of the FFQ is that it did not take drinking habits into account, so we cannot make any statements on the potential role of drinking patterns. Also no information on diet sodas or water was available, so no statements on these beverages can be made. Nevertheless, this will not have influenced the isocaloric substitution models, because only energy-containing beverages were taken into account in this analysis. Results from these isocaloric substitution models suggest that it is not

TABLE 5 Relative change in HTGC and 95% CIs per 1 serving/d of alcoholic beverage substitution by nonalcoholic beverage in participants of the Netherlands Epidemiology of Obesity study, men and women between 45 and 65 y of age with direct assessment of HTGC by proton magnetic resonance spectroscopy[1]

	Crude	Multivariable	Multivariable + TBF
Nonalcoholic beverages (total)			
Total	0.85 (0.81, 0.88)	0.89 (0.85, 0.93)	0.90 (0.86, 0.94)
Men	0.89 (0.85, 0.93)	0.90 (0.86, 0.95)	0.91 (0.87, 0.96)
Women	0.91 (0.83, 0.99)	0.87 (0.79, 0.95)	0.86 (0.80, 0.94)
Tea (without sugar or milk)[2]			
Total	0.81 (0.78, 0.85)	0.87 (0.83, 0.92)	0.89 (0.85, 0.94)
Men	0.88 (0.82, 0.94)	0.90 (0.84, 0.96)	0.92 (0.86, 0.99)
Women	0.88 (0.79, 0.97)	0.86 (0.78, 0.94)	0.86 (0.79, 0.94)
Coffee (without sugar or milk)[2]			
Total	0.85 (0.81, 0.89)	0.88 (0.84, 0.92)	0.88 (0.84, 0.92)
Men	0.89 (0.84, 0.94)	0.90 (0.85, 0.95)	0.91 (0.86, 0.96)
Women	0.88 (0.79, 0.97)	0.84 (0.76, 0.92)	0.83 (0.77, 0.91)
Milk[2]			
Total	0.86 (0.80, 0.92)	0.87 (0.81, 0.93)	0.88 (0.83, 0.94)
Men	0.83 (0.77, 0.91)	0.84 (0.77, 0.91)	0.86 (0.80, 0.92)
Women	0.94 (0.82, 1.09)	0.90 (0.78, 1.03)	0.89 (0.79, 1.00)
SSBs[2]			
Total	0.93 (0.87, 1.00)	0.98 (0.92, 1.04)	0.96 (0.91, 1.02)
Men	0.96 (0.89, 1.03)	1.00 (0.92, 1.08)	0.96 (0.90, 1.03)
Women	0.99 (0.88, 1.11)	0.95 (0.84, 1.06)	0.94 (0.85, 1.04)

[1] Multivariable analyses adjusted for age, sex, smoking, education, ethnicity, physical activity in leisure time, total energy intake of food, a sum variable of all beverages, and all beverages except for alcohol and itself. Results are based on analyses weighted towards the BMI distribution of the general population ($n = 1{,}966$), and derived from β coefficients with 95% CIs from linear regression analyses and expressed as a relative change. Such a ratio, for example 1.2, can be interpreted as 1.2 times HTGC for each extra serving per day, which would reflect an increase in HTGC from, for example, 5% to 6%. HTGC, hepatic TG content; SSB, sugar-sweetened beverage; TBF, total body fat.
[2] Servings equal 125 g for tea and coffee, 150 g for milk, and 150 g for SSBs.

energy per se, but possibly sugars that contribute to liver fat accumulation.

Alcohol is mainly metabolized in the liver (41) and can induce fatty liver by increasing fatty acid synthesis in the liver. Together with the impaired oxidation of these compounds caused by an increased accumulation of NAD(H), alcohol consumption may lead to increased TG synthesis, which is the main form of fat stored in the liver (42). Although many studies have investigated the association between light to moderate alcohol consumption and liver fat, results have been inconsistent and inconclusive and the exact mechanism remains unidentified. A prospective randomized study concluded that

TABLE 6 Relative change in HTGC and 95% CIs per 5 En% of alcoholic beverage substitution by nonalcoholic beverages in participants of the Netherlands Epidemiology of Obesity study, men and women between 45 and 65 y of age with direct assessment of HTGC by proton magnetic resonance spectroscopy[1]

	Crude	Multivariable	Multivariable + TBF
Nonalcoholic beverages (total)			
Total	0.91 (0.83, 0.98)	0.94 (0.87, 1.02)	0.94 (0.87, 1.01)
Men	0.90 (0.81, 1.00)	0.90 (0.81, 1.01)	0.88 (0.81, 0.97)
Women	0.99 (0.86, 1.14)	0.96 (0.84, 1.10)	0.96 (0.85, 1.09)
Milk			
Total	0.86 (0.77, 0.97)	0.88 (0.79, 0.98)	0.89 (0.81, 0.98)
Men	0.82 (0.71, 0.95)	0.80 (0.69, 0.92)	0.82 (0.72, 0.93)
Women	0.98 (0.82, 1.17)	0.94 (0.79, 1.13)	0.94 (0.81, 1.10)
SSBs			
Total	0.95 (0.85, 1.06)	1.01 (0.91, 1.12)	1.00 (0.91, 1.09)
Men	1.00 (0.86, 1.17)	1.04 (0.89, 1.22)	0.97 (0.85, 1.10)
Women	1.01 (0.87, 1.19)	0.98 (0.85, 1.14)	0.99 (0.86, 1.13)

[1] Multivariable analyses adjusted for age, sex, smoking, education, ethnicity, physical activity in leisure time, total energy intake from beverages, total energy intake from food, and all beverages except for alcohol and itself. Results are based on analyses weighted towards the BMI distribution of the general population ($n = 1{,}966$), and derived from β coefficients with 95% CIs from linear regression analyses and expressed as a relative change. Such a ratio, for example 1.2, can be interpreted as 1.2 times HTGC for each extra serving per day, which would reflect an increase in HTGC from, for example, 5% to 6%. En%, percent(age) of total energy intake; HTGC, hepatic TG content; SSB, sugar-sweetened beverage; TBF, total body fat.

moderate red wine consumption for 3 mo increased HTGC in subjects without steatosis at baseline (43), whereas red wine consumption for 4 wk in another randomized controlled trial did not significantly increase liver fat compared with de-alcoholized red wine (44). In addition, Ekstedt et al. (45) concluded from their long-term follow-up study that moderate alcohol consumption was associated with fibrosis progression in patients with NAFLD and that they should be advised to refrain from heavy episodic drinking. Modest wine consumption has been associated with reduced prevalence of suspected (NA)FLD in other studies (19, 21, 46, 47). In another study, light to moderate alcohol consumption had a potentially protective effect against insulin resistance in severely obese patients, but not on the severity of activity and stage of liver disease (48). Although in a recent review an association between moderate alcohol consumption and decreased NASH and fibrosis was shown, it was also observed that heavy episodic drinking may accelerate fibrosis progression (49). Most of the studies on alcohol consumption, however, including ours, did not take drinking habits into account, only the habitual total amount of alcohol consumed. However, even though certain drinking patterns such as drinking outside mealtimes and drinking multiple different alcoholic beverages lead to an increased risk of developing alcohol-related liver damage (50), it seems to be the cumulative consumption that is most strongly associated with the progression of alcoholic fatty liver disease (42). Although current literature is in disagreement about the role of moderate alcohol consumption, none of these studies performed substitution analysis to take into account that a person does not simply stop drinking alcohol but may replace the alcoholic beverages with other drinks. Moreover, results from a recent Mendelian randomization suggest that there is no beneficial effect of moderate alcohol consumption on the severity of NAFLD (24). In our study, light and moderate alcohol consumption were not associated with less liver fat, which is in line with these findings.

In addition, isocaloric replacement of alcohol with milk was associated with less liver fat in our study. This indicates that it is not caloric intake per se that leads to liver fat accumulation. The exact mechanism behind the seemingly negative association between dairy and liver fat remains unknown, although it is in agreement with current literature. Established biomarkers of dietary dairy fat intake have been associated with higher hepatic and systemic insulin sensitivity, lower fasting glucose concentrations, and less liver fat (51). Moreover, higher low-fat fermented dairy product consumption has also been associated with a decreased risk of developing type 2 diabetes in a prospective study (52).

Importantly, isocaloric replacement of alcohol with SSB consumption was equally associated with liver fat. Taken together with our results on substitution with milk, this suggests a role for sugars in liver fat accumulation. Our results are in line with recent findings from the Framingham Heart Study that showed a significant dose–response relation between SSBs and fatty liver disease, but not for diet soda intake (27). However, replacement of SSBs with other beverages was not investigated in this study.

Multiple underlying mechanisms have been proposed through which SSBs might contribute to the development of diabetes and cardiometabolic diseases not only via overall weight gain, but also independently through the metabolic effects of constituent sugars (53). It has also been suggested that liquid foods lead to less satiety and more postprandial hunger (25). Consumption of SSBs has been shown to induce peaks in blood glucose and insulin concentrations, contributing to a high glycemic state, which is in turn associated with insulin resistance, diabetes, and coronary artery disease (53, 54). In the Netherlands, soft drinks are one of the main sources of fructose (55), which is mostly metabolized to lipids in the liver and might therefore lead to an increase in hepatic de novo lipogenesis (56, 57). In a recent trial, moderate fructose consumption for 12 wk increased liver fat despite only a small increase in weight and waist circumference (58). Moreover, chronic fructose consumption has been shown to decrease resting energy expenditure in a 10-wk trial (59). Our results support the current literature and suggest that both alcoholic beverages and SSBs may contribute to liver fat accumulation. However, in clinical practice, although patients with NAFLD are often advised not to consume alcoholic beverages (18), there are no clear guidelines about what they should replace these beverages with.

In conclusion, consumption of alcoholic beverages was associated with a higher liver fat content in a population-based cohort. Replacing a serving of alcoholic beverages with nonalcoholic beverages was associated with less liver fat. Importantly, in isocaloric replacement of alcoholic beverages, SSBs were equally associated with liver fat as were alcoholic beverages, suggesting that both alcohol and sugars may contribute to liver fat accumulation. Although intervention studies should confirm to what extent HTGC can actually be changed by altering drinking habits, it is advised to specify with what beverages alcoholic beverages should be replaced in clinical practice, such as non-energy-containing beverages or milk, but not SSBs.

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